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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/475,784	06/07/95	LIVINGSTON	P	43016-C/JPW/

HM12/0627

JOHN P WHITE
COOPER AND DUNHAM
1185 AVENUE OF THE AMERICAS
NEW YORK NY 10036

EXAMINER	
DUFFY,P	
ART UNIT	**PAPER NUMBER**
1645	25

DATE MAILED: 06/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/475,784	Livingston et al
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 4-5-00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 78-100 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 78-100. is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

Response to Amendment

1. The amendment filed 4-5-00 has been entered into the record. Claims 78-100 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. The examiner notes the cancellation of claims 18-20 obviates the confusion as to the status of these claims.

4. The provisional rejection of the claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over all the claims of copending Application Nos. 08/481,809 is withdrawn because the claims in the '809 application are now drawn to oligosaccharide conjugates.

5. The rejection of claims 53, 55-57 and 59-77 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn based on applicants amendment to recite that the ganglioside is conjugated at the C-4 carbon of the sphingosine moiety of the ceramide to the ε-aminolysyl group of KLH.

6. The rejection of claims 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn based on the cancellation of these claims.

7. The rejection of claims 18-20, 53, 55-67 and 69-72 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al.(Immunobiol, 182:32-43, 1990) and further in view of Kensil et al and Marciani et al. is withdrawn based on the cancellation of the claims.

8. The rejection of claim 68 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Livingston et al (Cancer Research, 149:7045-7050, 1989, Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) as applied to claims 53-67, and 69-72 above and further in view of Irie et al is withdrawn based on based on cancellation of the claim.

Objections or Rejections Maintained

Specification

9. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

10. New claims 78-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the new claims 78-115 of

copending Application No. 08/477,097 for reasons previously made of record for claims 53, 55-57 and 59-77.

Applicants assert that the added new claims in the copending application obviate the obvious type double patenting. Applicants' arguments are not persuasive since the instantly claimed GM2-KLH conjugate and methods anticipates the corresponding GM2-KLH conjugate and methods of use thereof in the copending 08/477,097 application. Applicants amendments are insufficient to remove the rejection.

11. New claims 78-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application Nos. 08/477,147 for reasons previously made of record for claims 53, 55-57 and 59-77..

Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions. The instant conjugate species of GM2, GM3, GD3, GD3 lacone, o-acetyl GD3 and GT3 and methods of use thereof anticipate the conjugates and methods of the 08/477,147 application, inasmuch as, the '154 application claims GM2-KLH conjugates and methods of use. Applicants' amendments are insufficient to overcome the double patenting rejection.

12. New Claims 78-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of application No 08/196,154 for reasons previously made of record for claims 53, 55-57 and 59-77.

The instantly claimed compositions drawn to the specific species of GM2 ganglioside conjugated to KLH, anticipates all the pending claims of 08/196,154, inasmuch as the '154 application claims GM2-KLH conjugates and methods of use.

13. New claims 78-81 and 83-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 10/06/99 (see Paper No. 20) for claims 53-57, 59-72 and new claims 73-77 and the Office Action mailed 10-5-99.

As to claims 78-81 and 83-100, Applicants' arguments' and amendments have been carefully considered. The claims still recite "derivatives of KLH". Such derivatives are not enabled for reasons already made of record. Applicants' arguments and amendments are insufficient to obviate this rejection.

As to new claims 94-100, the claims are enabled for the use of the composition only for the treatment of cancer but are NOT enabled for the prevention of cancer, for reasons made of record in Paper No. 8, mailed 6-13-96. Applicants' arguments have been carefully considered but are not persuasive. Applicants' argue that the conjugate vaccine of the invention prevents outgrowth of micrometastases and prevents cancer *per se* (Zhang et al, Cancer Research 58:2844-2849, 1998). This is not persuasive, the claims are not drawn to preventing outgrowth of micrometastases and the conjugate used in the paper is GD2-KLH (10 ug of GD2 conjugated

to 60 ug KLH, wherein the conjugation of GD2 to KLH was achieved by conversion of the GD2 ceramide double bond to aldehyde by ozonolysis and attachment to KLH by reductive amination in the presence of cyanoborohydride) plus 10 ug QS-21. Thus, the conjugate of the claims is not that which has been demonstrated by the art prevents outgrowth of micrometastases, nor does the method provide for the method of the paper (multiple doses administered by a specific route. Moreover, the article specifically teach that the vaccine "... should be used exclusively in the adjuvant setting, where circulating tumor cells and micrometastases are the primary targets (page 2844, last line of abstract)." The evidence of the paper targeted circulating cells specific type of tumor cell (lymphoma) which was administered intravenously and micrometastases thereof from circulation, which is clearly not representative of cancers or relapses as instantly claimed. Moreover, Figure 1, demonstrates that administration of the GD2-KLH, QS-21 vaccine at days -21, -14 and -7 does not prevent cancer as demonstrated by the death of some of the experimental group after experimental intravenous challenge of lymphoma cells (see Figure 1, Experiments 3 and 6B). At page 2845, column 2, second and third paragraph, Zhang et al teach that the vaccine prolonged survival, but in the discussion of experiment 6, only 4 out of 6 vaccinated mice remained disease free at the latest time point measured. Moreover, Zhang et al admit that the alleged protection in Experiment 7 of Figure 1, was " not statistically significant" and moreover this experiment is not directly comparable with the other experiments because the tumor burden administered intravenously was substantially reduced. Clearly the vaccine when administered prior to the cancer does not prevent as claimed or as argued by applicants. Additionally, prevention of relapse as claimed has not been demonstrated nor specifically addressed by this paper and Zhang et al admits that "If antibodies of sufficient titer and potency to eliminate circulating cancer cells and micrometastases could be maintained in cancer patients

as well, even metastatic cancer would have quite a different implication. With continuing showers of metastases no longer possible, aggressive treatment of primary and metastatic sites might result in long term control." Relapsing of cancer is quite different than elimination of micrometastases and the paper only addresses circulating syngeneic tumor lymphoma cells and micrometastases (see page 2848, column 1, last paragraph) not primary cancer. Zhang et al do not address primary cancer and the experimental protocols set forth therein do not address prevention of primary cancer as is claimed for prevention of relapse of cancer. Reduction of circulating lymphoma cells and reduction in micrometastases is not commensurate in scope with prevention of cancer or prevention of a relapse of cancer.

The rejection is maintained.

Claim Rejections - 35 USC § 103

14. New claims 78-95 and 97-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is maintained for reasons made of record for previous claims 18-20, 53, 55-67 and 69-72 in Paper No. 23, 10-5-99.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. This is not persuasive, the conjugation procedure as combined provides for the identical procedure as

Applicants' coupling procedure. Moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the prior art would not arrived at the claimed product and methods. Applicants arguments are not persuasive and the rejection stands across the new claims.

15. New claim 114 is rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 69-81 and 83-96 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931) for reasons made of record for claim 68 in Paper No. 23, 10-5-99.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. This is not persuasive, the conjugation procedure as combined provides for the identical procedure as Applicants' coupling procedure. Moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the

prior art would not arrived at the claimed product and methods. Applicants' arguments are not persuasive and the rejection stands across the new claims.

Status of Claims

16. All claims stand rejected.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
June 22, 2000

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600